

REMARKS

~~Respectfully submitted,~~

Dated: August 15, 2001

Appendix A: marked up versions of amendments to specification showing the changes made

At page 49, replace the paragraph starting at line 1 with the following paragraph:

β -Aryl- β -alanines were prepared in a one-pot reaction. In brief, to a solution of a substituted benzaldehyde in absolute ethanol was added malonic acid and excess ammonium acetate, and the reaction mixture was heated to reflux. The reaction mixture was cooled to yield a mixture of the β -aryl- β -alanine and (in certain cases) a cinnamic acid derivative. The cinnamic acid (if present) was removed by acid/base extraction of the mixture to yield the β -aryl- β -alanine, often in moderate to good yield. The process is depicted in Figure 3, and further details of experimental procedures for the synthesis of certain β -aryl- β -alanine compounds are provided *infra*. A representative purification scheme for purifying the compounds is shown in Figure 4. Certain compounds prepared as described herein are set forth in Table 1, *infra*. Yield data are presented in two columns, the second being identical to that in Table 2, *infra*.

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At page 50, replace Table 1 with the following Table:

Table 1. β -aryl- β -alanines prepared from benzaldehydes.

| Compound RCH(NH ₂)CH ₂ COOH | Yield (%) | <u>Yield (%)</u> (from Table 2) |
|--|-----------|------------------------------------|
| R = | | |
| 4-Fluorophenyl | 68.5% | <u>61.5%</u> |
| 4-Phenoxyphenyl | 39.7% | <u>68.1%</u> |
| <u>3-(4-methylphenoxy)phenyl</u> [3-Methylphenyl] | 56.4% | <u>56.4%</u> |
| 3-Methyl-4-methoxyphenyl | 52.7% | <u>52.7%</u> |
| 3-(3,4-dichlorophenoxy)phenyl | 32.6% | <u>42.6%</u> |
| 2-Methylphenyl | 19.0% | <u>19.0%</u> |
| 3-(4-chlorophenoxy)phenyl | 23.2% | <u>33.2%</u> |
| 2,5-Dimethyl-4-methoxyphenyl | 12.6% | <u>22.6%</u> |
| 4-Trifluoromethoxyphenyl | 15.2% | <u>46.2%</u> |
| 2-Chlorophenyl | 21.7% | <u>27.7%</u> |
| 2-Fluoro-3-trifluoromethylphenyl | 5.5% | <u>15.5%</u> |
| 3-Bromo-4-methoxyphenyl | 23.8% | <u>43.8%</u> |
| 4-Bromophenyl | 34.2% | <u>69.2%</u> |
| Phenyl | 61.1% | <u>67.1%</u> |
| 4-Methylphenyl | 51% | <u>51.0%</u> |
| 4-Chlorophenyl | 12% | <u>65.0%</u> |
| 4-Acetamidophenyl | 23% | <u>23.0%</u> |
| 2,5-Dimethoxyphenyl | 22% | <u>22.0%</u> |
| 4-Diethylaminophenyl | | |
| 3-Methylphenyl | 45.4% | <u>45.8%</u> |
| 2-Hydroxy-3-methoxyphenyl | 11% | <u>17.2%</u> |
| 4-Phenylphenyl | 40.2% | <u>40.2%</u> |
| 3,4-Dibenzyloxyphenyl | 36.2% | <u>36.2%</u> |
| 3-[(3-Trifluoromethyl)phenoxy]phenyl | 29.7% | <u>39.7%</u> |

At page 52, replace the paragraph starting at line 23 with the following paragraph:

Additional compounds as synthesized generally in accordance with the previous paragraphs, and analytical data therefor are provided below in Table 2.

At page 69, replace the paragraph starting at line 31 with the following paragraph:

The compounds of the invention listed in Tables 2 and 3, *supra*, were tested for biological activity per Example 6. The following compounds were found to have at least weak activity: β -p-methylphenyl- β -alanine hydrochloride, β -2-hydroxy-3-methoxyphenyl- β -alanine, β -3-methyl-4-methoxyphenyl- β -alanine (slight), β -3-(3,4-dichlorophenoxy)phenyl- β -alanine hydrochloride (moderate), β -2,5-dimethyl-4-methoxyphenyl- β -alanine, β -p-(trifluoromethoxy)phenyl- β -alanine, and β -2-fluoro-3-(trifluoromethyl)phenyl- β -alanine (moderate).

At page 70, replace the paragraph starting at line 22 with the following paragraph:

Example 6

Selected compounds were dissolved in 0.9% NaCl or suspended in a mixture of 30% polyethylene glycol 400 and 70% water, and tested in an animal model. Briefly, the compounds were administered intraperitoneally or orally to carsworth Farms #1 mice (in a volume of 0.01 ml/g of body weight) or Sprague-Dawley rats (in a volume of 0.004 ml/g body weight). Times on peak effect and peak neurologic deficit were determined before the anticonvulsant tests were administered.

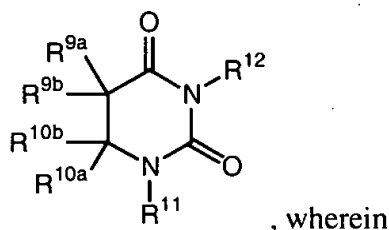
At page 71, replace the paragraph starting at line 11 with the following paragraph:

Example 7

Testing of the dioxapiperazine compounds was performed in 12 mice at doses of 30, 100, 300 mg/kg (4 mice each) 30 minutes and four hours after the test compounds was administered. The results are shown in Table 4.

Appendix B: marked up version of the claims showing the changes made

68. (new) A method for inhibiting epileptogenesis, comprising administering to a subject in need thereof an effective amount of a compound represented by the formula:



- R^{9a}, R^{9b}, R^{10a}, R^{10b} are each independently hydrogen, an alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxy carbonyloxy, or aminocarbonyl group, or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; or
- R^{9a} and R^{9b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or one of R^{9a} and R^{9b} is joined with one of R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R¹¹ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxy carbonyl; or one of R^{10a} and R^{10b} is joined with R¹¹, together with the carbon atom and nitrogen atom to which they are respectively attached, to form a heterocyclic ring having from 4 to 8 members in the ring; and

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- R¹² is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate;

or a pharmaceutically acceptable salt thereof; such that epileptogenesis is inhibited.

69. (new) The method of inhibiting epileptogenesis according to claim 1 wherein

- R^{9a}, R^{9b}, R^{10a}, and R^{10b} are independently hydrogen or an alkyl, cycloalkyl, aryl, alkoxy, or aryloxy group; or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; and
- R¹¹ and R¹² are each independently hydrogen, alkyl, or alkylcarbonyl.

70. (new) The method of inhibiting epileptogenesis according to claim 2 wherein R¹¹ and R¹² are hydrogen.

71. (new) The method of inhibiting epileptogenesis according to claim 2 wherein said R^{9a}, R^{9b}, R^{10a}, R^{10b}, R¹¹, or R¹² alkyl or alkyloxy group has a straight or branched chain alkyl group having 20 or fewer carbon atoms in the backbone.

72. (new) The method of inhibiting epileptogenesis according to claim 4 wherein said alkyl group is substituted.

73. (new) The method of inhibiting epileptogenesis according to claim 5 wherein said alkyl group is substituted with an aryl group.

74. (new) The method of inhibiting epileptogenesis according to claim 2 wherein said R^{9a}, R^{9b}, R^{10a}, or R^{10b} cycloalkyl group has 4 to 10 carbon atoms in the ring structure.

75. (new) The method of inhibiting epileptogenesis according to claim 7 wherein said cycloalkyl group is substituted.

76. (new) The method of inhibiting epileptogenesis according to claim 8 wherein said cycloalkyl substituent is a *tert*-butyl or phenyl group.

77. (new) The method of inhibiting epileptogenesis according to claim 2 wherein said aryl or said aryloxy group is substituted.

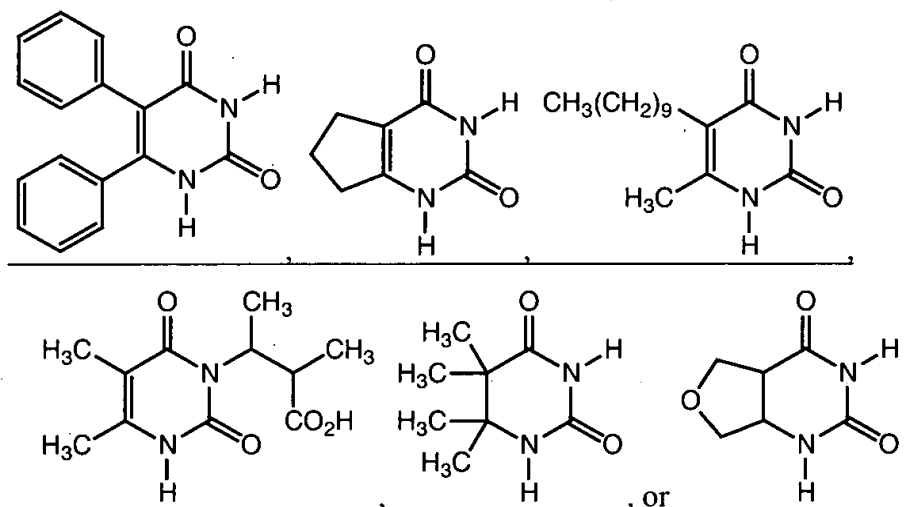
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78. (new) The method of inhibiting epileptogenesis according to claim 6 wherein said aryl group is substituted.
79. (new) The method of inhibiting epileptogenesis according to claim 10 wherein said aryl or aryloxy substitution is a halogen, hydroxyl, alkyl, alkoxy, amino, aryloxy, alkyl amino, dialkylamino, arylamino, alkylcarbonylamino, or an aromatic moiety.
80. (new) The method of inhibiting epileptogenesis according to claim 11 wherein said aryl substitution is a halogen, hydroxyl, alkyl, alkoxy, amino, aryloxy, alkyl amino, dialkylamino, arylamino, alkylcarbonylamino, or an aromatic moiety.
81. (new) The method of inhibiting epileptogenesis according to claim 12 wherein said aromatic moiety is a phenyl, naphthyl, quinolyl, or indolyl group.
82. (new) The method of inhibiting epileptogenesis according to claim 13 wherein said aromatic moiety is a phenyl, naphthyl, quinolyl, or indolyl group.
83. (new) The method of inhibiting epileptogenesis according to claim 14 wherein said phenyl group is substituted.
84. (new) The method of inhibiting epileptogenesis according to claim 15 wherein said phenyl group is substituted.
85. (new) The method of inhibiting epileptogenesis according to claim 16 wherein said substituted phenyl group is a 4-fluorophenyl, 4-phenoxyphenyl, 3-(4-methylphenoxy)phenyl, 3-methyl-4-methoxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-methylphenyl, 3-(4-chlorophenoxy)phenyl, 2,5-dimethyl-4-methoxyphenyl, 4-trifluoromethoxyphenyl, 2-chlorophenyl, 2-fluoro-3-trifluoromethylphenyl, 3-bromo-4-methoxyphenyl, 4-bromophenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl, 2,5-dimethoxyphenyl, 4-diethylaminophenyl, 3-methylphenyl, 2-hydroxy-3-methoxyphenyl, 4-phenylphenyl, 3,4-dibenzoyloxyphenyl, or a 3-[(3-trifluoromethyl)phenyloxy]phenyl group.

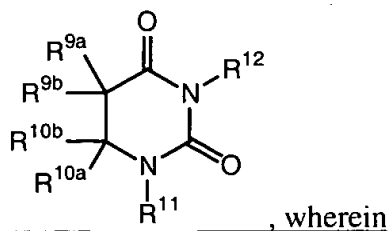
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86. (new) The method of inhibiting epileptogenesis according to claim 17 wherein said substituted phenyl group is a 4-fluorophenyl, 4-phenoxyphenyl, 3-(4-methylphenoxy)phenyl, 3-methyl-4-methoxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-methylphenyl, 3-(4-chlorophenoxy)phenyl, 2,5-dimethyl-4-methoxyphenyl, 4-trifluoromethoxyphenyl, 2-chlorophenyl, 2-fluoro-3-trifluoromethylphenyl, 3-bromo-4-methoxyphenyl, 4-bromophenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl, 2,5-dimethoxyphenyl, 4-diethylaminophenyl, 3-methylphenyl, 2-hydroxy-3-methoxyphenyl, 4-phenylphenyl, 3,4-dibenzyloxyphenyl, or a 3-[(3-trifluoromethyl)phenoxy]phenyl group.

87. (new) A method of inhibiting epileptogenesis according to claim 1 wherein said compound is



88. (new) A method for treating a convulsive disorder, comprising administering to a subject in need thereof an effective amount of a compound represented by the formula:



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- R^{9a}, R^{9b}, R^{10a}, R^{10b} are each independently hydrogen, an alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxy carbonyloxy, or aminocarbonyl group, or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; or
- R^{9a} and R^{9b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or one of R^{9a} and R^{9b} is joined with one of R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R¹¹ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxy carbonyl; or one of R^{10b} and R^{10b} is joined with R¹¹, together with the carbon atom and nitrogen atom to which they are respectively attached, to form a heterocyclic ring having from 4 to 8 members in the ring; and
- R¹² is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate;

or a pharmaceutically acceptable salt thereof; such that said convulsive disorder is treated.

89. (new) The method of claim 21, wherein said compound is a substituted or unsubstituted uracil, dihydrouracil or β -ureidopropionate compound, or a derivative, analog, or a pharmaceutically acceptable salt thereof.

90. (new) The method of claim 22, wherein said uracil is a derivative selected from the group consisting of substituted pyrimidines, UMP and uridine, or analogs thereof.

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